**IN THE UNITED STATES DISTRICT COURT**
**FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA**
**AT CHARLESTON**

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| **IN RE ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION** | **Master File No. 2:12-MD-02327**<br>**MDL 2327** |
| **THIS DOCUMENT RELATES TO:**<br>**WAVE 1 CASES** | **JOSEPH R. GOODWIN**<br>**U.S. DISTRICT JUDGE** |

**MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE THE OPINIONS AND TESTIMONY OF DR. VLADIMIR IAKOVLEV**

Ethicon, Inc. and Johnson & Johnson (collectively, "Ethicon"), submit this memorandum in support of their motion to exclude the testimony of Dr. Vladimir Iakovlev. Recent scientific testing and medical literature establish that Dr. Iakovlev's methodology cannot withstand *Daubert* scrutiny. Ethicon requests a hearing pursuant to Federal Rules of Evidence 104(a) and 104(c) to demonstrate that Plaintiffs cannot meet their burden of establishing the admissibility of Dr. Iakovlev's testimony. The cases to which this motion applies are identified in Ex. A.

## INTRODUCTION

Dr. Iakovlev is a pathologist who Plaintiffs retained as an expert witness. Although the Court has permitted Dr. Iakovlev to testify in prior cases against Ethicon,[1] recent scientific literature and testing prove Dr. Iakovlev's methodology is improper.

Dr. Iakovlev has admitted that the central premise of his degradation opinions — that Prolene degrades *in vivo* causing it to traps stains in its degraded surface that are detectable using

[1] *See* Mem. Op. and Order (*Daubert* Motions), at 27, *Bellew v. Ethicon, Inc*., No. 2:13-cv-22473 (S.D.W. Va. Nov. 20, 2014) [Doc # 265]; *Edwards v. Ethicon, Inc.*, No. 2:12-cv-09972, 2014 WL 3361923, at *24 (S.D.W. Va. Jul. 8, 2014).

light microscopy — is a testable hypothesis. Dr. Iakovlev admits he has failed to conduct the tests necessary to prove his theory. *See* Ex. B, Iakovlev 3/21/16 *Stubblefield* Dep. Tr. 64:19–65:4.

Ethicon's experts, however, have tested Dr. Iakovlev's hypothesis using reliable scientific methods and have *disproven* his theory. Ethicon's experts intentionally oxidized Prolene using two different approaches, applied the same sample preparation protocol and stains used by Dr. Iakovlev, and proved that oxidized Prolene cannot hold stain.

Thus, not only is Dr. Iakovlev's core opinion — that stained "bark" around a fiber was oxidized Prolene — unsupported by testing or scientific literature, but Ethicon's experts have proven that it is fundamentally flawed. Moreover, Dr. Iakovlev's own recently published studies confirm that the degradation opinions he seeks to offer at trial, as well as his opinions regarding the complications allegedly caused by degradation, are unsupported by scientific literature and inconsistent with his out-of-court publications.

Dr. Iakovlev's opinions regarding the complications allegedly caused by Ethicon mesh products are similarly flawed. For instance, one of Dr. Iakovlev's proposed biological mechanisms — that degradation causes increased inflammation and that this increased inflammation leads to pain — is also a testable hypothesis. Yet again, Dr. Iakovlev has never tested this hypothesis as he has never examined asymptomatic mesh explants and compared them to symptomatic mesh explants. Other experts, however, have assessed this theory and have proven that increased levels of inflammation in pelvic tissue are not correlated with increased pain. *See* Ex. C, A. Hill, *et al.*, *Histopathology of Excised Midurethral Sling Mesh*, 26 Int'l Urogyncology J. 591 (2015). Thus, Dr. Iakovlev's theoretical biological mechanism has been disproven, but he has conducted no testing to counter these results.

Dr. Iakovlev's opinions about complications are also inconsistent with (i) relevant scientific literature, (ii) his own publications, and (iii) basic facts of anatomy and physiology. Indeed, he admitted at deposition that his complication opinions are estimates of probability, not conclusions offered to a reasonable degree of medical certainty. He has also admitted that he failed to consider a statistically significant, asymptomatic comparator in his analysis, which deprives his opinions of reliability.

As Ethicon's expert gynecological pathologist and neuropathologists explain, Dr. Iakovlev's failure to adhere to a legitimate scientific methodology renders his causation opinions unreliable. For example, while Dr. Iakovlev seeks to offer numerous opinions that Ethicon mesh products cause pain in women, his opinions are based on his faulty understanding of the basic structure and function of nerves. Similarly, Dr. Iakovlev's opinion that every patient who experiences an erosion also suffers from an infection is pure speculation — he has made no effort to adhere to the standard criteria used by the medical community to determine whether an infection exists.

Dr. Iakovlev overreaches in basing his opinions on light microscopy and histological stains, as these tools do not permit even neuropathologists to make the sorts of conclusions regarding nerves and pain that Dr. Iakovlev seeks to offer in this case. Additionally, Dr. Iakovlev's opinions regarding mesh deformation and his novel "compartmentalization" theory are unsupported by scientific data or literature and inconsistent with medical facts as to the female anatomy.

Finally, Dr. Iakovlev seeks to explain many of his opinions regarding Ethicon's mesh products using various meshes not at issue in this litigation. Indeed, Dr. Iakovlev has admitted at

deposition that he received many of these meshes from plaintiffs' counsel in other pelvic mesh litigation, rather than from the Plaintiffs in this case.

## ARGUMENT

### I. Legal Standard

Ethicon incorporates by reference the standard of review for *Daubert* motions articulated by the Court in *Edwards v. Ethicon, Inc.*, No. 2:12-CV-09972, 2014 WL 3361923, at **1–3 (S.D.W. Va. July 8, 2014).

### II. The Court Should Exclude Dr. Iakovlev's Degradation Opinions.

#### A. Dr. Iakovlev's Degradation Opinions Are Based On A Hypothesis He Has Not Tested.

##### i. Dr. Iakovlev's reliance on an untested hypothesis is inconsistent with the scientific method.

Dr. Iakovlev's degradation opinions are based on a testable hypothesis that he admits he has failed to test. The central theory underlying all of Dr. Iakovlev's degradation opinions is that the Prolene in Ethicon mesh products degrades *in vivo* creating cracks in the degraded Prolene that trap histological stains, which Dr. Iakovlev can detect via light microscopy. *See* Ex. D, Expert Report of Dr. Vladimir Iakovlev ("Iakovlev Report"), at 8–9, 18–19 (discussing degradation theories). He claims to detect a degraded "bark" around the fiber after staining. All of his other degradation-related opinions are dependent on this purported observation. Because Dr. Iakovlev has not tested whether degraded Prolene can trap stain and this theory is not supported by scientific literature, Dr. Iakovlev's degradation opinions are nothing but speculation.

Dr. Iakovlev concedes that his hypothesis is capable of being tested by intentionally oxidizing pristine Prolene polypropylene to determine (i) whether it degrades and, if so, (ii) whether the intentionally oxidized and degraded polypropylene holds stain. *See* Ex. E,

Iakovlev 9/11/15 Dep. Tr. 31:14–46:13 (discussing Dr. Iakovlev's testing to determine whether oxidized Prolene traps stain). In fact, Dr. Iakovlev testified in September 2015 that he was conducting a test to prove his hypothesis by placing pristine Prolene in an oxidative medium to intentionally induce oxidation so he can later test whether the oxidized Prolene holds stain.[2] *Id.*

Significantly, however, he admitted that his "test is still in progress." *See id.* at 31:14–25 ("I haven't examined [the mesh samples] yet"). At that time, he claimed he would not have the results of that test for many months because he claims it takes at least 18 months to obtain the level of degradation or oxidation necessary for the Prolene polypropylene to retain the stain. *Id.* at 40:19–41:8; 35:14–18.[3] As recently as March 21, 2016, Dr. Iakovlev testified that he has chosen not to conduct the test at all. *See* Ex. B, Iakovlev 3/21/16 *Stubblefield* Dep. Tr. 64:19–65:4.

Dr. Iakovlev's admission is striking — he concedes he has presented an untested conclusion.[4] Thus, the foundational premise upon which all of Dr. Iakovlev's degradation

[2] Dr. Iakovlev is aware that Dr. Scott Guelcher, another expert for Plaintiffs, has conducted a test to determine if Prolene is subject to *in vitro* oxidation. Ex. E, Iakovlev 9/11/15 Dep. Tr. 40:19–42:3. Indeed, Drs. Iakovlev and Guelcher are co-authors of a paper discussing Dr. Iakovlev's degradation opinions, including his bark theory. Ex. F, V. Iakovlev, *et al.*, *Degradation of Polypropylene* In Vivo: *A Microscopic Analysis of Meshes Explanted From Patients*, J. Biomed. Mater. Res. Part B (2015). Yet, Dr. Iakovlev refuses to test his hypothesis using mesh allegedly oxidized through Dr. Guelcher's protocol because he believes Dr. Guelcher's six-week test is not long enough for the fibers to oxidize. *See* Ex. E, Iakovlev 9/11/15 Dep. Tr. 40:19–42:3. Dr. Guelcher is the subject of a separate challenge filed by Ethicon in this case. Ultimately, neither Dr. Iakovlev nor Dr. Guelcher can reasonably conclude that Prolene will oxidize and hold stain, because neither has actually tested that hypothesis.

[3] Dr. Iakovlev's testimony regarding the amount of time required for degradation to become visible using his techniques is remarkable for its inconsistency. *Compare* Ex. G, Iakovlev 4/19/16 *Ramirez* Dep. Tr. 394:15–21 (testifying that degradation appears at 1 year), *with* Ex. H, Iakovlev 3/4/16 *Vignos-Ware* Dep. Tr. 39:11–24 (testifying that he observed degradation in a mesh that was explanted at eight months).

[4] The lack of reliability of Dr. Iakovlev's opinions is highlighted by his failure to conform his testing to the scientific method. Dr. Iakovlev admitted that he did not prepare a protocol, and

opinions rest is merely a hypothesis that has been disproven. As Judge Posner explained, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). The Court should preclude Dr. Iakovlev from offering his untested bark theory at trial on this basis alone.

**ii. Ethicon's experts have disproven Dr. Iakovlev's hypothesis.**

In order to test the validity of Dr. Iakovlev's theory, Ethicon retained expert witnesses from Exponent who followed appropriate scientific methodology and tested his hypothesis. *See* Ex. I, Expert Report of Dr. Steven MacLean. To do so, Exponent intentionally oxidized Prolene mesh samples, and then applied the same histological stains used by Dr. Iakovlev to the samples to determine whether the Prolene retained the stain. *See id.* at 54–68. Specifically, Exponent intentionally oxidized Prolene mesh samples using two different approaches: (i) exposure to ultraviolet radiation, and (ii) exposure to the oxidative medium used by Drs. Scott Guelcher and Russell Dunn, experts for plaintiffs in pelvic mesh litigation. *Id.* at 54–56. Exponent's analysis of the meshes using both approaches proved that even intentionally oxidized Prolene does not trap histological stain. *Id.* at 57–61.

In addition, Exponent's investigation proved that the bark-like outer layer surrounding Prolene fibers in Dr. Iakovlev's images is the result of various imaging artifacts. *Id.* at 63–68. Among other things, Exponent's analysis demonstrated the following:

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instead merely consulted a study regarding preparation of the oxidative medium. *See* Ex. E, Iakovlev 9/11/15 Dep. Tr. 32:24–33:6. Dr. Iakovlev does not have any lab documentation or an inventory for this testing. *Id.* at 35:2–13. He could not identify the meshes being tested, *id.* at 34:21–35:1, and did not know how many pieces of mesh he is testing, *id.* at 32:9–12. Although he claims that he followed a study to prepare the oxidative medium, Dr. Iakovlev could not explain its composition. *Id.* at 34:5–14. As this Court has explained, "[v]igorous adherence to protocols and controls are the hallmarks of 'good science.'" *Sanchez v. Bos. Sci. Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 (S.D.W. Va. Oct. 17, 2014) (citation omitted).

- Shading and other artifacts can be produced by manipulating a microscope's polarizers when viewing the fibers. *See id.* at 64–65 (explaining that slides for microscopy are prepared using a microtome to slice the mesh fibers, which causes variations in the thickness of the fibers in the slide which "can create edge artifacts under polarized light").

- The appearance of a purple hue in some of Dr. Iakovlev's images is the product of exposing the specimen to plane-polarized light. *See id.* at 66.

- Differences in the material density between a sample and its surroundings can cause the appearance of lines that seem to separate the two substances, and which can be altered by changing the focus of the microscope. *See id.* at 65–66.

- The sample preparation process can result in differences in fiber thickness in individual fiber samples which, in turn, can cause stains to collect in pockets between the fiber and glass slide. *See id.* at 63–64. When viewed through a microscope, these pockets of stain create the illusion that the fiber sample is stained. *See id.* at 64.

Thus, Exponent—using a valid, documented, and repeatable scientific methodology — has established that Dr. Iakovlev's methods are flawed.

This is not a case of mere disagreement between the results offered by the parties' respective experts. Dr. Iakovlev has not presented *results*; he has offered only a *hypothesis* which is untested (inexplicably, even he will not test it), unsupported by scientific literature (as discussed below), and ultimately inconsistent with the scientific method. *See Claar v. Burlington N. R.R.*, 29 F.3d 499, 502–03 (9th Cir.1994) ("Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method."). Conversely, Exponent applied the scientific method to Dr. Iakovlev's hypothesis and has proved that his degradation opinion is the product of flawed methodology.[5]

[5] Notably, Exponent's work based on this testing methodology has been accepted without revision for publication and presentation in a peer-reviewed conference proceeding by the Society of Plastics Engineers. Ex. J, MacLean 4/18/16 Dep. Tr. 129:22-131:18; *see also* Ex. K, MacLean 4/18/16 Dep. Tr. Ex. 20, S. Benight, *et al.*, *Microscopy of Intentionally Oxidized Polypropylene-Based Mesh Material* (forthcoming May 2016). Specifically, the forthcoming study reports Exponent's procedures, data, and findings from its testing conducted in connection with *Mullins v. Ethicon*. *Id.* at 130:12–17.

For all of these reasons, the Court should preclude Dr. Iakovlev from testifying about this disproven theory.

**B. Dr. Iakovlev's Degradation Theory Is Neither Based In, Nor Supported By, Scientific Literature.**

Dr. Iakovlev has stated in his writings and testimony that he is the first person to propose the theory that degraded Prolene traps stain observable using light microscopy. *See* Ex. L, V. Iakovlev, *et al.*, *Pathology of Explanted Transvaginal Meshes*, 8 Int'l J. Med., Health, Pharm. and Biomed. Engineering 512 (2014) ("The degradation bark is easily visible by routine microscopy, yet escaped pathologists for over 50 years."); *see also* Ex. M, Iakovlev 12/17/14 *In re Bos. Sci.* Dep. Tr. 194:4–6 ("I'm the first one who is describing light microscopy features of polypropylene degradation."). Dr. Iakovlev admits that his theory is not based in prior studies. *See* Ex. E, Iakovlev 9/11/15 Dep. Tr. 36:10–16 (explaining that he did not consult anyone for his oxidation testing because "[n]obody did it before").

Dr. Iakovlev also admits that there is no published scientific literature describing degradation bark in polypropylene other than his own. *See* Ex. F, Iakovlev, *Degradation of Polypropylene* In Vivo, at 7 ("[W]e found no description of these findings in published literature after a search through online and printed sources."); *see also* Ex. N, Iakovlev 3/18/14 Dep. Tr. 275:8–13. Indeed, a review paper co-authored by Dr. Iakovlev recognizes that "the question of whether polypropylene degrades *in vivo* has not been fully resolved, despite decades of use." Ex. O, Blaivas, *et al.*, *Safety Considerations for Synthetic Sling Surgery*, Nature Reviews Urology 17 (2015).

Given the dearth of scientific literature supporting his theory, and the fact that his own writings question the existence of *in vivo* degradation, it cannot be said that Dr. Iakovlev's novel theory has garnered general acceptance by the scientific community. *See* Ex. M, Iakovlev

12/17/14 *In re Bos. Sci.* Dep. Tr. 239:15–240:2 (admitting that his own article is the only published paper reporting that degraded polypropylene traps histological dyes); *see also* Ex. P, Expert Report of Juan C. Felix, M.D. ("Felix Report") 27 (explaining that "the methodology of identifying degraded polypropylene using stains used for biologic tissue is not accepted by the majority of experts in the field" because histology "[s]tains such as H&E work by attaching to structures with different ionic charges," and "are not trapped like a cup would hold water"). Accordingly, the Court should preclude Dr. Iakovlev from testifying in this case.

This is exactly what *Daubert*'s gate-keeping function is designed to address. Dr. Iakovlev's theories are unproven junk science and do not meet the threshold for admissibility. Given the complexity of these issues, there is no way to know if vigorous cross-examination is sufficient to cure Dr. Iakovlev's scientifically flawed opinions. Because of the methodological flaws inherent in Dr. Iakovlev's opinions, they should not be considered by the jury due to the significant risk of confusion and misunderstanding of these technical scientific principles. *In re Digitek Prods. Liab. Litig.*, 821 F. Supp. 2d 822, 839 (S.D.W. Va. 2011) (an expert's opinions are inadmissible as "inconsistent with good science" if he makes "overreaching or speculative conclusions . . . based upon overreaching or speculative methodologies").

### C. Dr. Iakovlev's Opinion That Degradation Causes Clinical Complications Is Unreliable.

It is inappropriate and unethical for an expert to represent to the scientific community that a specific biological mechanism is unproven while simultaneously representing in litigation that the fact is proven. In this case, Dr. Iakovlev plans to tell the jury that it is proven that degradation of Prolene implanted in women causes various complications. Specifically, Dr. Iakovlev's Report states that "degradation needs to be considered as a factor of additional stiffening and late deformations of the mesh," and that "if chemical and physical properties of a material change

while it is in the body it should not be used for permanent applications and for anatomical sites from which the devices cannot be safely removed." Ex. D, Iakovlev Report at 8–9.

However, Dr. Iakovlev's scientific writings tell a far different story. In his publications, Dr. Iakovlev concedes that the question of whether the alleged degradation of polypropylene causes clinical complications in patients remains open. For instance:

- Dr. Iakovlev explained that his "discovery" of degradation using stains and light microscopy merely "*opens the door to study* the role of degradation in the development of complications." Ex. Q, V. Iakovlev, *et al.*, In Vivo *Degradation of Surgical Polypropylene Meshes: A Finding Overlooked For Decades*, 465 Virchows Arch (2014), at 35 (emphasis added); *see also* Ex. R, V. Iakovlev, *Explanted Surgical Meshes: What Pathologists and Industry Failed to Do for 50 Years*, 465 Virchows 337 (2014) ("The newly described findings *need to be studied* in correlation with clinical symptoms to guide future developments.") (emphasis added).

- In an article co-authored by Dr. Iakovlev, he was unwilling to assert that a causal connection exists between degradation and clinical effects. *See* Ex. L, V. Iakovlev, *et al.*, *Pathology of Explanted Transvaginal Meshes* 512 (2014) ("Polypropylene degradation *may play a role* in the continuous inflammatory response, mesh hardening, and late deformations" and the "chemical products of degradation *need to be studied* for their composition and effect on the tissue.") (emphasis added).

- Dr. Iakovlev expressly admitted that the "exact mechanisms of these late complications are yet to be understood" in a recent paper authored with Dr. Guelcher. *See* Ex. F, Iakovlev, *Degradation of Polypropylene* In Vivo at 10.

- Finally, as noted above, Dr. Iakovlev acknowledges in a recent review paper that "the question of whether polypropylene degrades *in vivo* has not been fully resolved, despite decades of use." Ex. O, Blaivas at 17.

The Court should not permit Dr. Iakovlev to opine at trial that degradation of Prolene causes complications when his publications (which are subject to peer review and critique) do not make such a causal connection, and even cast doubt on the proposition that degradation occurs *in vivo*. *See Kumho*, 526 U.S. at 152 (explaining that an expert must "employ[] in the

courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.").[6]

## III. The Court Should Exclude Dr. Iakovlev's Opinions Regarding Complications As Unreliable.

### A. Dr. Iakovlev's analysis is unreliable because he failed to use a control.

Dr. Iakovlev's opinions that Ethicon mesh products cause complications in women are based on his histological analysis of explanted meshes. As Ethicon's expert gynecological pathologists and neuropathologists in this case have explained, Dr. Iakovlev's opinions are inconsistent with the scientific method because he failed to compare his histological observations to an asymptomatic comparator. *See* Ex. P, Felix Report at 11–12; Ex. S, Expert Report of Teri Longacre 4–5; Ex. T, Expert Report of Roger McLendon ("McLendon Report") ¶ 6; Ex. U, Expert Report of Hannes Vogel ("Vogel Report") 14. Dr. Iakovlev's failure to use a control means that he cannot eliminate the likelihood that the histological presentation of women suffering from pain is the same as the histology of women not suffering from pain. *See* Ex. P, Felix Report at 12; Ex. U, Vogel Report at 14.

This is a significant gap in Dr. Iakovlev's analysis because if the histology of both groups is the same, his histological findings cannot identify the cause of the pain. *See* Ex. P, Felix Report at 12. The same holds true with respect to all of the complications to which Dr. Iakovlev opines. Without a proper control, Dr. Iakovlev's attempt to correlate specific complications with samples of explanted Ethicon mesh products is nothing but conjecture. *See Sanchez v. Bos. Sci.*

[6] The disparity between Dr. Iakovlev's opinions regarding Prolene in litigation and his out-of-court conduct is highlighted by his testimony regarding his efforts to address the alleged risks posed by Prolene at his hospital. Specifically, he claims that he reported the results of his research to a hernia surgeon and a urogynecologist, but refused to identify those individuals. *See* Ex. E, Iakovlev 9/11/15 Depo Tr. 80:23–81:6; 81:10–82:4. He also acknowledged that he has taken no other steps to stop his hospital from using Prolene sutures or Prolene mesh in patients. *Id.* at 84:20–25. He admitted that the hospital continues to use Prolene sutures and probably uses Prolene mesh for patients that he treats. *Id.* at 80:17–19; 82:5–15.

*Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 (S.D.W. Va. Oct. 17, 2014) ("Vigorous adherence to protocols and controls are the hallmarks of 'good science.'").

**B. Dr. Iakovlev ignores relevant scientific literature.**

Dr. Iakovlev failed to account for scientific literature relevant to his opinions. As Dr. Felix explained, "clinical pathological correlations cannot be made" in the absence of a "body of evidence demonstrating [that] histology is associated with clinical symptomotology." *See* Ex. P, Felix Report at 12. In Dr. Iakovlev's review article, he states that "[a]fter >50 years of use, only a few published studies exist in which investigators actually examined histological changes in mesh explants that had been removed from humans." *See* Ex. O, Blaivas, at 15. The only studies he identifies are three hernia mesh papers authored by other experts for plaintiffs in pelvic mesh litigation and a study examining mesh from a single patient. *Id.* Notably, however, Dr. Iakovlev did not cite or discuss Dr. Hill's *Histopathology of Excised Midurethral Sling Mesh*, 26 Int'l Urogyncology J. 591 (2015) in his Report or publications.

Indeed, Dr. Iakovlev was unaware of the existence of the Hill study until counsel for Ethicon identified it for him at deposition in the *Mullins* case. *See* Ex. E, Iakovlev 9/11/15 Dep. Tr. 152:14–153:8 (testifying that the only studies he found in a literature search for studies comparing histology for meshes removed for pain against meshes removed for non-pain reasons addressed hernia repair). Even now, Dr. Iakovlev simply dismisses the Hill study based on his unsupported assertion that the study was not "done appropriately enough to be a reliable source," and because the authors "didn't do analysis the way [he] do[es]." Ex. V, Iakovlev 11/5/15 *Carlino* Dep. Tr. 60:19–62:10. Tellingly, however, Dr. Iakovlev has never identified any authority supporting his claims regarding the reliability of the Hill study.

Dr. Iakovlev's failure to address the findings of the Hill study is significant because it bears directly on his opinions in this case. The Hill study conducted the analysis that

Dr. Iakovlev has never done—*i.e.*, using a control and comparing the histological reaction of symptomatic and asymptomatic meshes. Specifically, Dr. Iakovlev opines that Ethicon mesh products cause inflammation and fibrosis following implantation, and that these conditions cause pain in women implanted with Ethicon mesh products. *See* Ex. D, Iakovlev Report at 15–16. The Hill study examined 130 explanted meshes, and conducted a histological comparison of the patients who complained of pain and those who did not. Ex. C, A. Hill, *et al.*, *Histopathology of Excised Midurethral Sling Mesh*, 26 Int'l Urogyncology J. 591, 592 (2015). Contrary to their own hypothesis, the authors found that pain was *not* associated with increased inflammation. *Id.* at 592–93. The authors also found no difference in fibrosis between the two groups. *Id.* at 593.

As Ethicon's experts explain in their expert reports, Dr. Iakovlev's failure to account for the Hill study is not an isolated incident. *See, e.g.*, Ex. T, McLendon Report at ¶ 8 (explaining that Dr. Iakovlev's "[s]tatements relating pain pathogenesis to fibrous tissue about the mesh fail to explain why published studies reporting microscopic findings of post-operative meshes reveal a normal number and density of nerve fibers in the tissue.")[7]; Ex. T, McLendon Report at ¶ 10 (Dr. Iakovlev's opinion that mesh-related inflammation causes pain fails to account for a study finding fewer inflammatory cells and fibroblasts, as well as unchanged numbers of granulocytes, lymphocytes, and monocytes in pre-op transvaginal biopsies than post-op)[8]; Ex. P, Felix Report at 16 (Dr. Iakovlev's opinion that scar tissue associated with mesh contracts during maturation, leading to compression of tissues and organs is "clinically unfounded based on [a] compilation of

[7] Dr. McLendon cites to Ex. W, R. Bendavid, *et al.*, *Mesh-related SIN Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain*, 5 Int'l J. Clinical Med. 799 (2014).

[8] Dr. McLendon cites to Ex. X, C. Elmer, *et al.*, *Histological Inflammatory Response to Transvaginal Polypropylene Mesh for Pelvic Reconstructive Surgery*, 181 J. Urology 1189 (2009).

clinical studies in meta-analyses").[9] The Court should not permit Dr. Iakovlev to offer his histological observations as evidence that Ethicon mesh products cause complications where he failed to consider scientific literature directly relevant to his opinions.

**C. Dr. Iakovlev's own paper reveals that his methodology is not scientifically legitimate.**

A review paper co-authored by Dr. Iakovlev confirms that, outside of the context of litigation, he understands that his approach is inadequate. Specifically, the paper states that "[s]everal studies have confirmed" that "when microscopy [is] performed, results of the microscopic examinations usually d[o] not explain the specific complications experienced by the patients." Ex. O, Blaivas at 15. The paper explains that "general human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications." *Id.*

The Court should preclude Dr. Iakovlev from testifying because his own writings show that his methodology in this case is an insufficient basis for making causal conclusions. *See Kumho*, 526 U.S. at 152 (explaining that an expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.").[10]

**D. Dr. Iakovlev's opinions are speculative.**

Although his own paper stated that the review of histology is insufficient to correlate complications to mesh usage, Dr. Iakovlev would do just that in this case. At deposition,

[9] Dr. Felix cites to Ex. Y, M. Schmipf, *et al.*, *Sling Surgery for Stress Urinary Incontinence in Women: A Systematic Review and Metaanalysis*, 211 Am. J. Obstetetric Gynecology 71.e1 (2014) and Ex. Z, A. Ford, *et al.*, *Mid-Urethral Sling Operations for Stress Urinary Incontinence in Women*, Cochrane Database of Systematic Reviews (2015).

[10] As further evidence of the lack of reliability of Dr. Iakovlev's opinions, he has admitted at deposition that he alters the images used in his expert reports using Photoshop software. *See* Ex. V, Iakovlev 11/5/15 *Carlino* Dep. Tr. 110:1–117:9. Specifically, he changes the images to reflect what he believes to be consistent with what he sees in the microscope. *Id.* at 111:15–112:8. Dr. Iakovlev has not provided original images to Ethicon for comparison.

however, Dr. Iakovlev has admitted that he could not draw causal conclusions based on his review of histological slides; instead, he "can only estimate the probability." Ex. E, Iakovlev 9/11/15 Dep. Tr. 140:14–141:8; *see also id.* at 159:2-160:4 (acknowledging that he could not rule out that a "deformed" nerve did not cause pain because "there are many, many, many factors which cause" symptoms); *id.* at 208:25–209:22 (admitting that he cannot opine that mesh caused symptoms in a specific slide because "[c]inical symptoms is [sic] a multifactorial, complex phenomena" but "probability that it will compress urethra is higher"); *id.* at 224:9–225:3 (claiming mesh fibers "[p]robably" irritated the nerve in the slide, but refusing to say the mesh "actually caused symptoms"). Dr. Iakovlev's speculative conclusions are inconsistent with the scientific method, and should be excluded. *See In re Digitek*, 821 F. Supp. at 839.

**E. Dr. Iakovlev lacks specialized knowledge sufficient to testify regarding potential injuries to the female body.**

Dr. Iakovlev seeks to offer various opinions in this case as to how alleged defects in Ethicon mesh products cause complications in patients. But Ethicon's gynecological pathologist and neuropathologists explain that Dr. Iakovlev's opinions are predicated on fundamental errors of anatomy and physiology, as well as the manner in which nerves sense and transmit pain.

For example, Dr. Iakovlev's opinion that thromboses and occlusions of capillaries and arterioles are evidence of complications related to Ethicon mesh products, *see* Ex. D, Iakovlev Report at 17, 62–64, show that he is unaware that such features are "commonplace throughout the body and have never been shown to be associated with pain," *see* Ex. P, Felix Report at 23.

Additionally, although Dr. Iakovlev claims that connection of the Ethicon mesh products "to the smooth muscle of the vaginal wall can interfere with its contraction (intercourse etc.)," *see* Ex. D, Iakovlev Report at 17, striated muscles in the pelvis are responsible for contraction of

the vagina during intercourse and these muscles would not be affected by an implant, *see* Ex. P, Felix Report at 13.

Dr. Iakovlev also testified that the presence of smooth muscle in mesh pores reveals that the mesh has migrated because smooth muscle has a restricted ability to regenerate. *See* Ex. E, Iakovlev 9/11/15 Dep. Tr. 190:1–191:1. Dr. Iakovlev's statement is simply false. *See* Ex. P, Felix Report at 13–14 (explaining the "generally accepted fact" that "[s]mooth muscle is able to regenerate in response to injury, such as surgery").

These are not theories subject to interpretation, but facts generally accepted by the medical community. Dr. Iakovlev should not be permitted to opine that Ethicon mesh products cause complications on areas of the body about which he cannot provide specialized knowledge. *See Hines v. Wyeth*, No. 2:04-cv-0690, 2011 WL 2680842, at *7 (S.D.W. Va. July 8, 2011) (expert opinion must not go "beyond the expert[']s qualifications").

## IV. Dr. Iakovlev's Opinions Regarding Pain Are Inconsistent With The Scientific Method and Medical Facts.

Dr. Iakovlev is not a neuropathologist. Yet, he offers numerous opinions premised on the erroneous assumption that the presence of nerve twigs (microscopic branches of nerves) on histological slides are indicative of pain. He opines that the growth of nerves through and around mesh causes pain by direct mechanical irritation. *See* Ex. D, Iakovlev Report at 11–12; 15–16. Similarly, he asserts that the innervation of scar tissue formed due to Ethicon mesh products causes pain by "direct mechanical irritation of the nerves as well as irritation of the receptors by inflammatory and physical mechanisms of pain." *Id.* at 15. He also claims that the chronic inflammatory response caused by Ethicon mesh products results in an increased sensitivity for pain in the surrounding tissues. *Id.* at 16.

Dr. Iakovlev bases these opinions on his analysis of slides depicting nerve twigs adjacent to mesh and present in scar tissue. *See, e.g.*, *id.* at 24–30 (slides showing mesh and scar tissue); *id.* at 31–38 (slides showing innervation of mesh in the "scar plate"); *id.* at 44 (slides showing innervation of mucosa overlying mesh).

As Drs. Hannes Vogel and Roger McLendon — Ethicon's neuropathologists in this litigation — explain, Dr. Iakovlev's conclusion that the mere observation of a nerve twig in scar tissue or the proximity of a nerve to mesh are sufficient to conclude that the patient suffered from pain reveal both a flawed methodology and a misunderstanding of the basic structure and function of nerves. Nerves in the human body are specialized, and only sensory nerve fibers are capable of transmitting pain signals. *See* Ex. T, McLendon Report at 9 (explaining function of motor, autonomic, and sensory nerves); Ex. U, Vogel Report at 3–6 (same). Thus, one cannot link a specific nerve to pain without first determining that it is, in fact, a sensory nerve.

Even if it is a sensory nerve fiber, one must identify the sensory receptor to ascertain the type of signal that the nerve carries. *Id.* at 6; *see also id.* at 4 (explaining that sensory nerves carry different types of signals); Ex. T, McLendon Report at 9 (same). In addition, one cannot draw a conclusion regarding pain without identifying a sensory receptor, because these sensory receptors, not the nerve fiber itself, trigger the transmission of a pain signal. *Id.*; *see also id.* at ¶ 14; Ex. P, Felix Report at 22.

Dr. Iakovlev's reliance on light microscopy and immunohistochemical stains does not permit him to make causal conclusions regarding pain. Dr. Iakovlev bases his pain opinions on his review of histological slides at low power, and the use of S100 and neurofilament to identify nerves. Yet, as Dr. Vogel explained, even neuropathologists cannot differentiate between nerve types via light microscopy. *See* Ex. U, Vogel Report at 6. And while stains like S100 and

neurofilament help identify nerve parts, "specifically Schwann cells and axons, respectively," they cannot distinguish between nerve types and "do not identify sensory receptors." *Id*.

Dr. Iakovlev's lack of familiarity with the pathophysiology of nerves not only demonstrates a lack of specialized knowledge regarding the issues about which he seeks to testify, it contributed to his failure to apply a scientifically legitimate methodology for concluding that Ethicon mesh products cause pain in women.

Dr. Iakovlev's pain opinions are illustrative of the lack of a legitimate methodology underlying his opinions, but the inadequacies of his attempt to base causal conclusions on his histology apply with equal force to all of his opinions regarding the alleged complications caused by Ethicon mesh products. *See id.* at 7 (Dr. Iakovlev's "attribution of clinical symptoms to his histology is completely without reliable basis in the science of pathology.").

## V. Dr. Iakovlev's Opinion that the Presence of an Erosion Necessarily Implies that the Patient had a Wound Infection is Unreliable.

Dr. Iakovlev opines that Ethicon mesh products cause erosions in patients, and that the existence of an erosion necessarily implies that the patient has a wound infection. Specifically, Dr. Iakovlev has testified that "erosion is always associated with localized infection." *See* Ex. AA, Iakovlev 3/13/16 *McBrayer* Dep. Tr. 14:2–6; Ex. BB, Iakovlev 3/4/16 *Funderburke* Dep. Tr. 25:12 (same); *see also id.* at 24:17–25:21 (explaining that a "diagnosis was made [of] vaginal erosion, which comes together with infection"). Indeed, Dr. Iakovlev seeks to offer this opinion even in cases in which he did not examine the Plaintiff's explant. *See* Ex. AA, Iakovlev 3/13/16 *McBrayer* Dep. Tr. 13:16–22. Dr. Iakovlev's infection opinion is simply false.

The Centers for Disease Control and Prevention ("CDC") has developed specific criteria for determining whether an infection exists under a variety of circumstances. For example, in order to diagnose a post-operative surgical site infection ("SSI") in connection with an

implantable device, the CDC requires that the infection occur within 1 year of the implant,[11] and involve at least one of the following:

- Purulent drainage from the deep incision . . . [;]
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative[;]
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination[; or,]
- Diagnosis of a deep incisional SSI by a surgeon or attending physician.

CDC, Ex. DD, *Guideline for Prevention of Surgical Site Infection*, at 252 (1999) ("SSI Guidelines"). Similarly, in order to diagnose a soft-tissue infection, the CDC requires that the patient have (i) "organisms identified from tissue or drainage from affected site by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment"; (ii) "purulent drainage at affected site"; or (iii) an abscess or other evidence of infection on gross anatomic or histopathological exam." Ex. EE, CDC, *CDC/NHSN Surveillance Definitions for Specific Types of Infections*, at 17–25 (Jan. 2016) ("Infection Definitions").

Regardless as to how an infection is classified, certain criteria must be satisfied before an infection can be diagnosed. *See id.*; SSI Guidelines at 252; *see also* Ex. FF, Expert Report of Daniel Sexton at 8–11. Dr. Iakovlev made no such efforts in this litigation.

Dr. Iakovlev's "all erosions equal an infection" opinion is unreliable and speculative because he failed to apply the diagnostic guidelines for ascertaining the existence of an infection

[11] The CDC has advised that a replacement of the *Guideline for Prevention of Surgical Site Infection* (1999) is forthcoming, under which an infection must manifest within 90 days to satisfy the deep incisional SSI requirements. *See* Ex. CC, CDC, *Surgical Site Infection (SSI) Event*, at 9-1, 9-9.

defined by the CDC (or any other criteria). In fact, contrary to the generally accepted practice of the medical community, Dr. Iakovlev believes that no such analysis is necessary, because "it's a given that there is infection" any time there is an erosion. *See, e.g.*, Ex. BB, Iakovlev 3/4/16 *Funderburke* Dep. Tr. 24:17–25:21. Moreover, Dr. Iakovlev explained that he ignores medical records in his infection analysis based on his unsubstantiated belief that an infection will invariably accompany an erosion. *Id.* at 25:22–26:7 ("Maybe [a medical record regarding infection] is there but I wouldn't pay attention[.]").

Finally, Dr. Iakovlev's opinion ignores the fact that erosions are generally treated — and resolve — with topical estrogen cream without the use of antibiotics. In other words, Dr. Iakovlev's infection opinion simply makes no sense because the standard method employed by the medical community to treat erosions does not involve a course of action designed to treat an infection.

For all of these reasons, the Court should preclude Dr. Iakovlev from offering such unreliable and speculative opinions at trial.

**VI. Dr. Iakovlev's Opinions Regarding Mesh Folding/Deformation Are Unreliable.**

Dr. Iakovlev opines that mesh can fold or curl *in vivo*, and that such deformations can form "compartments." Ex. D, Iakovlev Report at 11, 17. He claims that mesh folding, curling, and compartments can cause pain. *Id.* at 11. But Dr. Iakovlev fails to identify any support for this novel theory. *See* Ex. U, Vogel Report at 14 (testifying that this theory is "unprecedented in the surgical or pathology medical literature regarding synthetic sling surgery").

Dr. Iakovlev's contention that he can look at a pathology slide and infer that mesh curled or deformed in the human body prior to explantation is similarly unfounded. As an initial matter, Dr. Iakovlev fails to follow the standard methodology used by pathologists for determining how a specimen is oriented in the human body. To ascertain how a specimen was oriented *in vivo*, a

pathologist must (i) identify anatomical landmarks, and (ii) consult markers provided by the explanting surgeon. Ex. GG, William Westra, *et al.*, Surgical Pathology Dissection 4 (2003); Ex. HH, Susan Lester, Manual of Surgical Pathology 7 (2010). Specifically, the surgeon must use sutures, tags, or a diagram to designate the orientation (*i.e.*, anterior, posterior, medial, lateral, superior, and inferior positioning) of the specimen. *See* Ex. GG, Westra at 4; Ex. HH, Lester at 7. The failure to adhere to this methodology at the time of explantation limits, if not eliminates, the pathologist's ability to determine the *in vivo* orientation of the specimen, and renders conclusions as to its *in vivo* appearance speculative. *See* Ex. GG, Westra at 4; Ex. HH, Lester at 7.

Dr. Iakovlev did not follow this methodology in developing his folding opinions. Rather, he simply concludes that a specimen that has a folded appearance during his examination was also folded *in vivo*. But as Dr. Maria Abadi — one of Ethicon's expert pathologists — explained, "if [a mesh] comes [out] folded, it has nothing to do with the way it was positioned *in vivo*," because the explanting surgeon subjects the explant to a variety of forces during the removal. *See* Ex. II, Abadi 3/31/16 Dep. Tr. 99:19–101:9 (explaining that without information from the surgeon, orientation of a specimen is "all speculation").

In addition, Dr. Iakovlev failed to consider that the highly elastic vaginal tissue into which Ethicon mesh products are implanted contracts immediately upon excision. *See* Ex. P, Felix Report at 24 (explaining that the fixation of the specimen in formalin will exacerbate any deformation). Finally, Dr. Iakovlev has admitted at deposition that he is unable to determine whether any alleged deformation occurs during the implantation procedure or *in vivo*. *See, e.g.*, Ex. E, Iakovlev 9/11/15 Dep. Tr. 213:12–24; 215:5–13; 216:20–24. Dr. Iakovlev's opinions regarding mesh curling or deformation are nothing but speculation and should be excluded.

Finally, Dr. Felix explained that Dr. Iakovlev's compartment theory is unsupported by data or literature, and that it simply makes no sense because the nerves, vessels, and tissue growing through the pore space cannot seal the pore in the manner Dr. Iakovlev suggests. *See* Ex. P, Felix Report at 18. Crucially, Dr. Iakovlev does not identify any mechanism, nerve receptor, or substance derived from inflammation to explain how these alleged compartments could cause pain. *See* Ex. U, Vogel Report at 14. Dr. Iakovlev's compartment theory is precisely the sort of novel theory that courts should exclude absent valid scientific support. *Rosen*, 78 F.3d at 319 ("the courtroom is not the place for scientific guesswork").

## VII. Dr. Iakovlev Should Not Be Permitted to Offer Opinions Based On Mesh Not At Issue In This Case Or Mesh That He Cannot Identify.

Dr. Iakovlev seeks to explain his opinions in this case using photographs of slides of mesh explants from various sources, many of which he has recycled from prior cases. *See* Ex. D, Iakovlev Report at 21–112. Yet, Dr. Iakovlev previously testified that he could not determine the origins of many of the slides used in his reports. Ex. E, Iakovlev 9/11/15 Dep. Tr. 107:15–109:5; *see also id.* at 20:22–21:22 (explaining that may have received some of his slides from Dr. Kreutzer, who had received them from plaintiffs' counsel in pelvic mesh litigation).

Dr. Iakovlev's opinions based on meshes not at issue in this litigation constitute the same sort of unreliable and irrelevant testimony that has been repeatedly excluded by this Court. *See, e.g.*, Ex. JJ, *Lewis v. Ethicon*, 2:12-cv-04301, MDL No. 2327, 2/12/14 Trial Tr. 18:19–19:3 (excluding evidence regarding Dr. Jordi's "additional explants"); *Lewis v. Ethicon*, 2014 U.S. Dist. LEXIS 15351 (S.D.W. Va. Jan. 15, 2014) (excluding Dr. Klinge's conclusions that were

drawn from samples "without any explanation of the method of selecting the [samples] or the potential error rate.").[12]

## CONCLUSION

For the foregoing reasons, Ethicon requests that the Court exclude the opinion testimony of Dr. Iakovlev, and issue an order for a hearing pursuant to Federal Rule of Civil Procedure 104 if necessary, and such other and further relief as the Court deems proper under the circumstances.

Respectfully submitted,

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[12] Plaintiffs in *Bellew* conceded that they would not question Dr. Iakovlev about the "about the other 130 surgical mesh explants he has analyzed prior to this case." Mem. Op. and Order at 27, *Bellew v. Ethicon, Inc*., No. 2:13-cv-22473 (S.D. W. Va. Nov. 20, 2014) [Doc. # 265].

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| **IN RE ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION** | **Master File No. 2:12-MD-02327 MDL 2327** |
| **THIS DOCUMENT RELATES TO: WAVE 1 CASES** | **JOSEPH R. GOODWIN U.S. DISTRICT JUDGE** |

**CERTIFICATE OF SERVICE**

I hereby certify that on April 21, 2016, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notification of such filing to CM/ECF participants registered to receive service in this MDL.

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